THE THIRD GENERATION CEPHALOSPORINS*

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THE cephalosporins are a unique group of beta-lactam antibiotics derived from cephalosporin C, which is produced by the fungus *Cephalosporium acremonium*. Cefoxitin is a member of the closely related family of beta-lactams, the cephamycins.[1] It is a derivative of cephamycin C, a product of the fungus *Streptomyces lactamdurans*. Chemically, the two classes of antibiotics are similar, the cephalomycins having one additional methoxy-group substituted on the lactam ring (Figure 1). Recently, totally synthetic compounds have been developed that are closely related to the cephalosporins. By substitution of an oxygen atom for the sulfur atom in the cephem nucleus, a group of antibiotics called oxa-B-lactams have been developed (Figure 1).[2,3] Moxalactam is the first oxa-B-lactam antibiotic released for clinical use. It has enhanced intrinsic activity against Gram-negative bacilli, as do other so-called "third generation cephalosporins", compared with early cephalosporins.[4] Moxalactam also takes advantage of the methoxy group found in cefoxitin, which makes it more resistant to B-lactamases.[1] Although technically not a true cephalosporin (in fact current production methods use penicillin G as the raw material from which it is synthesized), moxalactam has so many properties in common with the cephalosporins that it is most convenient to include it among the third generation cephalosporins.

At the present time, more than a dozen different cephalosporins are available in the United States. In an attempt to simplify the understanding of these, they are usually classified into three groups (Table I). The first generation cephalosporins were introduced in the early 1970s. These antibiotics are remarkably similar in their spectrum of activity, but differ

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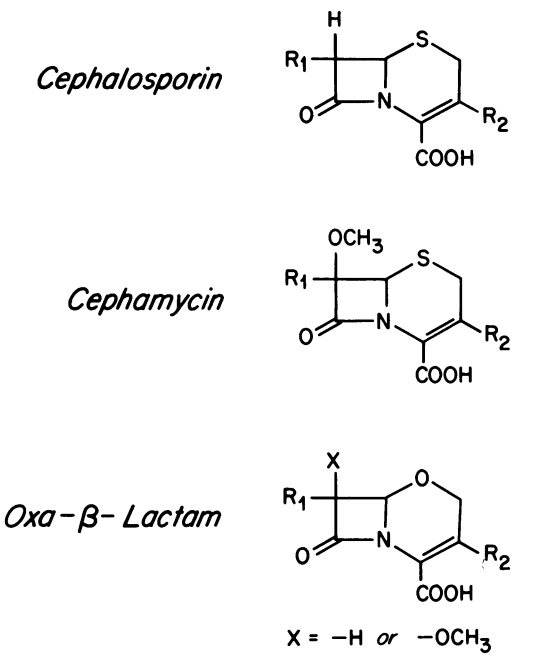

Fig. 1. Structural differences in the nuclei of the cephalosporins, cephamycins, and oxa-B-lactams

in pharmacokinetic properties and routes of administration.[5,6] Cephalothin, the first of the group to be introduced, rapidly became one of the most commonly used drugs in hospitalized patients. It is active against most staphylococci, pneumococci, and streptococci. In addition, most community-acquired *Escherichia coli; Klebsiella pneumoniae,* and *Proteus mirabilis* are susceptible.[5,6] Cephalexin has similar activity and is well absorbed orally. Cefadroxil was introduced later and, because of its longer serum half-life, extended the dosage interval to twice a day.[6] Alteration of the substituent at the three position of the dihydrothiazine ring of cephalexin led to the development of cefaclor. Although still considered a first-generation compound, it is more active against Gram-negative bacilli, *N. gonorrheae,* and *Hemophilus influenzae,* including β-lactamase-producing strains.[7] Major problems with first-generation cephalosporins include resistance among certain hospital-acquired Gram-negative bacilli, intrinsic lack of activity against *Pseudomonas sp., Serratia sp., Enterobacter sp.*, and *Bacteroides fragilis*[5] and inability to cross the blood-brain barrier.[8]

TABLE I. CLASSIFICATION OF THE CEPHALOSPORINS

First generation cephalosporins	*Route of administration*
Cephalothin	IM/IV
Cefazolin	IM/IV
Cephapirin	IM/IV
Cephradine	IM/IV/PO
Cephaloridine*	
Cephalexin	PO
Cefadroxil	PO
Cefaclor	PO
Cephaloglycine	PO
Second generation cephalosporins	
Cefamandole	IV/IM
Cefoxitin	IV/IM
Cefuroxime*	
Third generation cephalosporins	
Moxalactam	IV/IM
Cefotaxime	IV/IM
Cefoperazone*	IV/IM
Ceftizoxime*	IV/IM
Ceforanide*	IV/IM
Cefsulodin*	IV/IM
Ceftriaxone*	IV/IM
Ceftazidine	IV/IM

* Not available in the United States.

The second generation of cephalosporins include cefamandole, cefuroxime, and the cephamycin, cefoxitin. These drugs all possess enhanced activity against many cephalothin-resistant organisms.[9-12] Cefamandole is also effective against *Hemophilus influenzae*, including B-lactamase-producing strains and many *Enterobacter sp.*,[13-15] Cefoxitin has better activity against *Serratia marcescens* and the anaerobes, including *Bacteroides fragilis*.[12-16] The second generation antibiotics inhibit most streptococci, pneumococci, and beta-lactamase producing staphylococci at achievable serum concentrations, but cefoxitin is significantly less active than the first-generation drugs against these organisms.[1,17]

In 1981 the United States Food and Drug Administration approved two of the third generation cephalosporins—cefotaxime and moxalactam—for clinical use. These compounds take advantage of structure-activity relationships studied in the laboratory. They have excellent activity against a wide range of organisms, while maintaining the low toxic-therapeutic ratio characteristic of the earlier cephalosporins. At the present time cefotaxime and moxalactam are commercially available, and cefoperazone is expected

to be released shortly. In addition, ceftizoxime, ceforanide, and cefsulodin will probably be marketed in the United States along with several other compounds already undergoing clinical trials (ceftriaxone and ceftazidime).[18]

It will be difficult if not impossible for most physicians to keep track of the subtle differences between these drugs, but there is no question that the third generation drugs will have significant and lasting advantages over those already on the market. This article will attempt to summarize some of the available data regarding the use of these drugs.

Mechanism of Action

The mechanism of action of the cephalosporins is complex and not fully understood. Originally, it was thought that these drugs (along with penicillin and the other B-lactams) behaved as analogs of and inhibited the activity of the enzyme transpeptidase.[19] Inhibition of this enzyme was thought to prevent proper cross-linking of new subunits into the bacterial cell wall. The weakened cell wall in the presence of a normally growing cytoplasm eventually led to lysis and death. However, more recent studies have demonstrated that this theory is too simplistic. Most organisms have from four to seven penicillin-binding proteins in their outer cell membrane.[20] These proteins interact with the B-lactam antibiotics, which seems to initiate a complex series of events leading to inhibition of growth and, in many instances, cell death. In the case of the pneumococcus, this interaction seems to interfere with the inhibition of endogenous autolysins. Therefore, the antibiotic actually allows the organism to "self-destruct". In the case of group A streptococci, the interaction leads to death of the organisms without accompanying lysis. The binding proteins vary in their affinity for the various B-lactams[20], and alteration of these proteins may be responsible for some of the acquired or intrinsic resistance to certain antibiotics.

Mechanism of Resistance

The most common mechanism by which organisms developed resistance to the first-generation cephalosporins was production of beta-lactamase(s). Production of these enzymes is governed by chromosomal or plasmid DNA. Particularly common among Gram-negative bacilli, these enzymes cleave the B-lactam ring and inactivate the antibiotic. Gram-positive organisms produce similar enzymes (penicillinases), but these are

not particularly active against the cephalosporins and semisynthetic penicillins. The second generation cephalosporins are considerably more resistant to the various Gram-negative B-lactamases. Cefamandole, however, is less resistant than cefuroxime and cefoxitin.[6] Spontaneous mutants resistant to cefamandole or cefoxitin which do not produce beta-lactamase have been well described.[21] Hence, other mechanisms of resistance clearly exist. Alteration of penicillin-binding proteins may play a role in the intrinsic cephalosporin resistance of *Streptococcus faecalis*,[22] methicillin-resistant staphylococci, and *Pseudomonas aeruginosa*, which are also resistant to other B-lactam antibiotics.[23] The third generation cephalosporins are even more resistant to B-lactamase activity. Moxalactam is resistant to hydrolysis by all enzymes except PSE 2 and 3 elaborated by certain strains of *Pseudomonas aeruginosa*.[24,25] Cefotaxime can be cleaved by PSE 2 and 3, as well as the bacteroides B-lactamase.[25] Cefoperazone can be cleaved by all three of these, plus IIIA, a beta-lactamase produced by certain Gram-negative bacilli.[25] Recently, mutants resistant to moxalactam have been studied. These organisms prevent the antibiotic from penetrating their outer cell envelope. An alteration in one of the pore-forming proteins that normally serve to allow penetration of the cephalosporins into the cell appears to be responsible for this permeability barrier.[26] Of interest is that resistance to one of the third generation cephalosporins (e.g., cefotaxime) does not necessarily predict resistance to the others. This phenomenon will make susceptibility testing with these drugs in the clinical laboratory difficult because use of "class discs" for third generation cephalosporins is not currently contemplated by the Food and Drug Administration. It is unlikely that most laboratories will have the resources routinely to test all of these drugs.

Spectrum of Activity

The third generation cephalosporins have a very broad spectrum of activity. Cefotaxime, moxalactam, and cefoperazone are highly active against most Gram-negative bacilli, including: *E. coli, Serratia sp., Proteus sp., Providencia sp., Klebsiella sp., Enterobacter sp., Shigella sp.*, and *Salmonella sp.*[4,27,29] All three are more active on a weight basis than the aminoglycosides against many of these organisms. In addition, *Hemophilus influenzae, Neisseria gonorrheae,* and *N. meningitidis* are very sensitive. Although these antibiotics have similar spectra, differences exist. Cefoperazone is the most active against *Pseudomonas aeruginosa,*

and inhibits up to 85% of strains at achievable serum concentrations.[30] It is less active against *Enterobacter sp.*, and half of all *Bacteroides fragilis* are resistant.[30] Moxalactam has the best activity against *Bacteroides fragilis*, inhibiting more than 90% of all strains at low concentrations.[31] Cefotaxime is least active against *Pseudomonas aeruginosa*, but is more active than the others against the streptococci and methicillin-sensitive staphylococci. As was the case with cefoxitin, all have less activity than the first generation compounds against Gram-positive cocci. It is important to note that none of these drugs is effective against methicillin-resistant staphylococci and, like all of the cephalosporins, lack activity against enterococci. In addition, they have poor activity against *Listeria monocytogenes*. When combined with the aminoglycosides, these compounds exert synergistic activity against a variable number of strains of *Pseudomonas aeruginosa* and *Serratia marcescens*. Antagonism has not been reported with such concentrations.[32,33]

Several other cephalosporins are currently under clinical investigation. Ceftazidine is highly resistant to beta-lactamases and is more active against *Pseudomonas aeruginosa* than other compounds.[34] Cefsulodin also possesses antipseudomonas activity, but it is less active against many other Gram-negative bacilli.[34] It also lacks effectiveness against carbenicillin-resistant organisms.[34] Ceforanide has activity similar to the second generation cephalosporins.[35] It may prove useful because of its long half-life and ability to produce high serum concentrations after intramuscular administration.[36] Ceftizoxime is active *in vitro* against nonfermenting Gram-negative bacilli-including *Pseudomonas aeruginosa, Pseudomonas cepacia, Flavobacterium sp.*, and *Acinetobacter sp.*[37] Ceftriaxone has no enhanced activity against *Pseudomonas sp.* and no special advantage over other available third generation cephalosporins.[38]

PHARMACOKINETICS

Major properties of cefotaxime, moxalactam, and cefoperazone are listed in Table II. All three can be administered intramuscularly or intravenously, but are not absorbed orally. Moxalactam has the longest serum half-life, allowing doses to be administered every eight hours.[39] Cefoperazone has an intermediate half-life, and can also be given every eight hours.[40] Cefotaxime is generally given every four to six hours. Peak serum levels are highest with moxalactam, which probably reflects its smaller volume of distribution.[41] Cefotaxime is metabolized to a desacety-

TABLE II. PHARMACOKINETIC PROPERTIES OF THREE THIRD GENERATION "CEPHALOSPORINS"

	Cefotaxime	*Moxalactam*	*Cefoperazone*
Route of administration	IM/IV	IM/IV	IM/IV
Serum half-life (hrs.)	1.2	2.3	1.6
Peak serum levels:			
500 mg. IM	11	24	26
1,000 mg. IV	41	70	65
Metabolism	desacetylation	Insign.	Insign.
Excretion	Urine	Urine	Urine/bile
Adjustment in renal failure	Moderate	Moderate	None

Based on references 39 to 45

lated form in the liver, which is then excreted in the urine.[42] The desacetylated form has less antibacterial activity than cefotaxime. Cefoperazone is excreted in the bile, and therefore does not require dosage modification in the presence of renal failure.[42,43] Ceftriaxone has a particularly long biological half-life and this may allow administration on a 12-to-24-hour basis.[38] For most infections, daily doses of 3 to 8 grams of these agents should suffice. Larger doses have been safely utilized in patients with severe infections.

CLINICAL USE

Third generation cephalosporins have been used to treat a large number of patients with infections due to susceptible organisms. To date, clinical experience in the United States has been more extensive with moxalactam and cefotaxime than with cefoperazone. In general, all three have been effective in the therapy of pneumonia, bacteremia, and intraabdominal, biliary and urinary tract infections.[46-51] Infections caused by a wide range of Gram-negative and Gram-positive organisms have been treated, including many resistant to the aminoglycosides and older cephalosporins. As predicted by *in vitro* studies, therapy of *Pseudomonas aeruginosa* infections has been complicated by a significant failure rate and development of resistance.[51] Most data accumulated thus far are from uncontrolled trials. Several important questions remain to be answered. Does increased activity of the third generation antibiotics improve upon the clinical outcome compared with therapy with the first and second generation cephalosporins against susceptible organisms? Can these drugs be used alone to replace

combination therapy with B-lactams plus an aminoglycoside in the treatment of life-threatening infections, particularly in compromised hosts? Preliminary data suggest that cefotaxime and moxalactam may be effective as clindamycin and gentamicin in the therapy of intraabdominal surgical infections.[47,57] Finally, no studies comparing the efficacy of the various third generation drugs with each other exist. Because of their similarities, it will likely be difficult if not impossible to demonstrate significant differences in most clinical settings.

One of the most dramatic advances has been the use of third generation cephalosporins in the treatment of Gram-negative bacillary meningitis. The mortality of meningitis caused by *Escherichia coli, Klebsiella pneumoniae, Serratia marcescens*, and *Pseudomonas aeruginosa* is at least 70%.[52] Therapy with chloramphenicol has a high failure rate, perhaps due to its inability to provide bactericidal concentrations in the cerebrospinal fluid against these organisms.[52] Aminoglycosides do not achieve adequate levels in the spinal fluid when given intravenously to adults.[53] Intrathecal administration of aminoglycosides produces adequate bactericidal levels, but is cumbersome and not without hazard. In addition, the presence of ventriculitis in many patients may necessitate instillation of the antibiotic directly into the ventricle.[53] This approach has not been of value in neonatal meningitis caused by these organisms.[54] Both moxalactam and cefotaxime have been shown to penetrate into the cerebrospinal fluid of patients with meningitis in significant concentrations.[55] Cerebrospinal fluid concentrations of 2 to 15 μg./ml. have been measured in patients treated with cefotaxime, and 5 to 35 μg./ml. with moxalactam.[55,56] In addition, because of their marked activity against Gram-negative bacilli, these levels are well above the minimal bactericidal concentration for most strains. *Pseudomonas aeruginosa* is an exception because concentrations of 32 to 64 μg./ml. of cefotaxime or moxalactam are necessary to achieve bactericidal activity against many of these strains. Currently only moxalactam has received approval for treatment of Gram-negative meningitis. However, both moxalactam and cefotaxime have been used successfully to treat well over 100 patients. Cure rates have been excellent (~85%), a dramatic improvement compared with earlier series.[52,55] Greater experience is needed in the therapy of meningitis due to *Hemophilus influenzae* and such Gram-positive organisms as *Streptococcus pneumonia*. Evidence available suggests that both moxalactam and cefotaxime will be effective in meningitis due to both ampicillin-susceptible and ampicillin-resistant strains of *H. influenzae*. Although cefotaxime has greater intrinsic activity

than moxalactam against such Gram-positive organisms as *S. aureus* and *S. pneumonia*, neither is active enough to enable one to confidently predict that they would be generally effective against meningitis due to these organisms. Neither should be used in *Listeria monocytogenes* meningitis. Clinical trials are currently underway evaluating moxalactam in the therapy of meningitis in neonates and children.

Toxicity

As with earlier compounds, third generation cephalosporins are remarkably well tolerated. Pain on intramuscular injection and local phlebitis following intravenous administration are the most common problems. Minor gastrointestinal symptoms including diarrhea, nausea, and anorexia may occur, and pseudomembranous colitis has been reported.[57] The latter is not surprising because these compounds generally lack activity against *C. difficile*. Allergic reactions appear to occur at a rate similar to those of earlier compounds (~3%), and include skin rash and rare cases of anaphylaxis, urticaria, serum sickness, as well as neutropenia.[57,58] The incidence of reactions in those patients treated with moxalactam who have a history of penicillin allergy has been 5%.[57] As with other cephalosporins, it seems prudent to avoid these drugs in patients with a history of anaphylaxis or immediate hypersensitivity reactions to penicillin unless absolutely necessary.[5] It does seem reasonable to use these drugs in patients with a history of minor reaction to the penicillins (fever, rash, eosinophilia).

Other adverse reactions associated with the cephalosporins include development of a positive direct Coombs reaction, usually without accompanying hemolytic anemia. Unique to the second and third generation compounds has been the development of bleeding secondary to hypoprothrombinemia. This appears to be related to elimination of vitamin K-producing gut organisms, and can be avoided by use of parenteral vitamin K.[59,60] Impairment of platelet function can also occur with all the cephalosporins.[59,61] This is usually not clinically evident except in the presence of unusually high serum concentrations of these drugs.

Nephrotoxicity is very rare among patients treated with the cephalosporins (except for cephaloridine) alone, although interstitial nephritis can occur. Of great concern has been the possibility that the cephalosporins can potentiate aminoglycoside nephrotoxicity. A blind, prospective study does suggest that cephalothin may potentiate aminoglycoside nephrotox-

icity.[62] This phenomenon has been neither demonstrated nor well studied with second and third generation compounds.

Cefoperazone, moxalactam, and cefamandole have all been reported to produce disulfiram-like reactions after alcohol ingestion.[63,64,65] The reactions typically developed after several days of therapy, and consisted of flushing, headache, nausea, vomiting, and hypotension. The mechanism of this reaction appears to be an antibiotic-induced alteration in the metabolism of alcohol with increases in blood acetaldehyde concentrations.[66] Therefore, patients should be instructed to avoid using alcohol during and for at least three days following administration of these antibiotics.

Although not a true toxic effect of the antibiotics themselves, the problem of superinfection and overgrowth with nonsusceptible organisms shoud be addressed. In one series, five of 41 patients treated with moxalactam became colonized by enterococci, another four became infected (two bacteremias and two urinary tract infections).[67] A review of more than 2,000 patients treated with moxalactam revealed enterococcal superinfection in 2.1%.[68] The incidence was highest in the subgroup of patients with Foley catheters who were being treated for urinary tract infections. Superinfection with resistant *Pseudomonas aeruginosa, Enterobacter sp., Candida sp.*, and enterococci have also been reported with cefotaxime therapy.[64] Superinfections by resistant organisms, particularly the enterococcus, are not surprising. The broad spectrum of these antibiotics and their ability to suppress endogenous bowel flora allow for the selection and overgrowth of resistant organisms. In addition, many patients who receive these agents are critically ill, and have previously received multiple courses of other antibiotics. The total lack of activity of cephalosporins against the enterococcus make this a likely organism. Although the broad spectrum of these antibiotics makes them useful in the initial therapy of an infection prior to culture results, it obviously may be a double-edged sword. Therefore, it seems imprudent to employ these agents for the routine treatment of infections due to organisms susceptible to other less broad spectrum agents.

CONCLUSIONS: THE FUTURE

Third generation cephalosporins possess many characteristics of the ideal antibiotic. They are bactericidal, stable, nontoxic, produce excellent tissue levels, are highly active against most pathogens, and resist beta-

lactamase hydrolysis. Unfortunately, they are also very expensive. Typical costs per gram of antibiotic to the patient (including hospital "markup") are: $4.00 for the first generation compounds, $9.00 for the second generation drugs, and $18 to $20 for the third generation cephalosporins. Certainly such expenses are justified in the therapy of bacillary Gram-negative meningitis. In addition, if it is demonstrated that these agents can be used as single agents in situations when combinations of more toxic antimicrobials are currently utilized, they will prove cost-effective. Preliminary data suggest that this may be the case in certain circumstances.[47] At the present time, their routine use cannot be justified, and they should be reserved to treat Gram-negative bacillary meningitis and other infections caused by susceptible organisms resistant to the less costly beta-lactams.

Third generation cephalosporins are a credit to the abilities of medical chemists. They were designed and synthesized with close attention to structural-functional relationships. The sheer number of new compounds currently undergoing investigation is staggering. In addition to the cephalosporins, a number of other beta-lactams are being developed for clinical use, including piperacillin, azlocillin, mezlocillin, N-formimidoyl thienamycin, and specific inhibitors of beta-lactamase such as clavulanic acid. It is impossible (and impractical) for practicing physicians to become familiar with more than one or two antibiotics from each class. Knowledge of the subtle difference between many of these will, of necessity, remain in the domain of infectious disease specialists.

SUMMARY

In 1981 the United States Food and Drug Administration approved the first of the third generation cephalosporins for clinical use. The introduction of cefotaxime was quickly followed by moxalactam, a synthetic oxa-B-lactam, and cefoperazone is expected to be released shortly. In addition, at least five other new cephalosporins are currently undergoing clinical trials. In general, these compounds have markedly enhanced activity against many Gram-negative organisms, including: *E. coli, Klebsiella sp., Serratia sp., Proteus sp., Providencia sp., Enterobacter sp., Shigella sp., H. influenzae*, and some strains of *Pseudomonas aeruginosa*. Moxalactam also inhibits virtually all strains of bacteroides. All these drugs can be given intravenously or intramuscularly, but none are absorbed orally. Clinical experience has confirmed that they are effective in the treatment

of many types of infection due to susceptible organisms. Cefotaxime and moxalactam both cross the blood-brain barrier in significant concentrations, and have improved the outcome of bacillary Gram-negative meningitis. It is likely that the third generation cephalosporins will replace more toxic combinations of antimicrobials in many clinical settings. However, at present their use should be limited to the therapy of bacillary Gram-negative meningitis and infections caused by organisms resistant to the less expensive cephalosporins.

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